Targeted Derivatization of Medicines via Novel C–H Functionalization

Research Thesis

Presented in partial fulfillment of the requirements for graduation with
Research Distinction in Biochemistry

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December 2015

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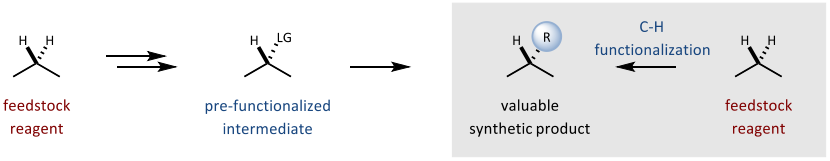
ABSTRACT

The most ubiquitous bond in pharmaceuticals rests between carbon and hydrogen and until recently, however, the C-H bond has been ignored as a target for synthetic manipulation because of its inherently inert nature and the significant energetic barrier associated with bond breakage. The utilization of C-H bonds as a means of activation for desired functional groups reduces multi-step syntheses to a single reaction, which drastically diminishes classical labor- and resource-intensive strategies for the production of complex molecules. Additionally, structural analogs of multifaceted, biologically active molecules can easily be obtained without having to individually construct each member of a library of substrates from scratch. This innovative process may be applied to potential anti-cancer drug candidates to increase their potency, effectivity, and bioactivity by targeted functionalization, which may allow for an accelerated opportunity to discover enhanced medicines directly from abundant precursors. The initial hypothesis for this C–H directed reaction was derived from the radical-based mechanism of the Hofmann-Löffler-Freytag reaction. As a way of generalizing this protocol to medicines, it has been sought to exclude the harsh halogenation typically required for the sequential 1,5-hydrogen shift and cyclization. Thus far, a method has been devised to directly cyclize amines to create a five-membered pyrrolidine ring from unbiased long-chain amine substrates through the generation of iodine in situ via mild reagents. Our research is currently focused on optimization and generalization of this method to explore a variety of substrates that offer medicinal relevance. This development of direct C–H activation has numerous applications in the medicinal, chemical, and biological target elucidation and offers a rewarding potential for increased efficacy in modern synthetic strategies.

INTRODUCTION

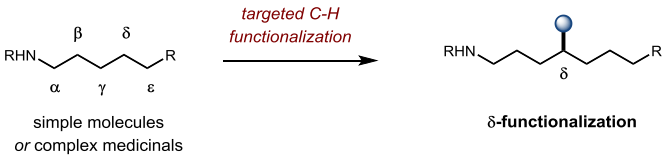
Since the initial discovery that the activation of inert carbon-hydrogen (C-H) bonds of alkane molecules may undergo functionalization in the 1980's, intense research efforts have devoted their focus into the exploration and utilization of this method as a means towards innovative and non-classical synthetic strategies.[1] C-H bonds, because of their intrinsically inactive nature and immense activation energy, have been overlooked as direct sites of functionalization. However, the activation of said "unreactive" bonds results in a drastic reduction from classical multi-step synthesis to a single reaction, furthermore diminishing the labor and resource expenditures in the production of complex molecules. Additionally, structural analogs of desired products may be more easily obtained by generating the ability to selectively target a number of various C-H bonds, without having to individually construct each substrate.

Figure 1. Direct C-H Functionalization as Compared with Classical Synthetic Strategies.



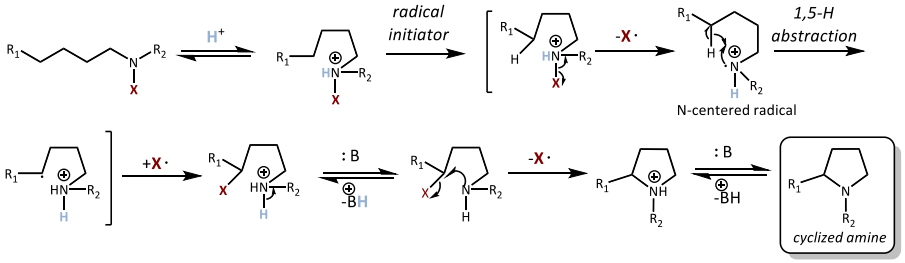
The initial direction of this project lay in the aspiration to generate a nitrate ester on the aliphatic chain of a protected amine at the δ-carbon by radical-trapping, utilizing a known reagent that requires rather mild conditions and is shown to be far less toxic than many other reagents in its category to perform C-H activation.[2] The idea was to screen a number of oxidants with varying inherent chemical properties on a multitude of amine substrates in the hope of creating a δ-functionalization.

Figure 2. Direct C-H Functionalization of Tosyl-Protected Heptylamine.



The inspiration for this research derived from the radical-based mechanism of the Hofmann-Löffler-Freytag (HLF) reaction, although it digresses from the original reaction through the modification of the conditions to a milder methodology in the elimination of the harsh halogenation followed by successive cyclization, while maintaining the δ-carbon specificity.[3]

Figure 3. Mechanism of the Hofmann-Löffler-Freytag reaction.

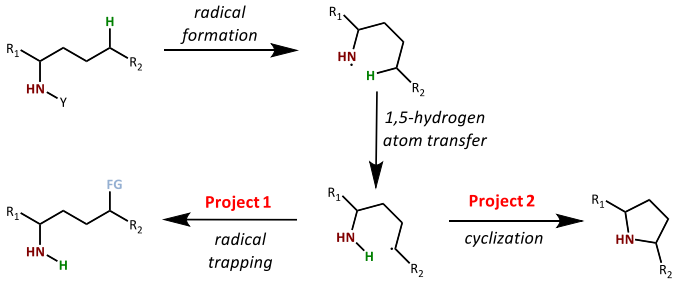


This interrupted approach to a viably established single-electron reaction in organic chemistry would represent one of the first halogen-free HLF type reaction, which has led to an exciting discovery with a multitude of possible applications. This novel exploration into a radical-centered reaction has scarcely been investigated because of the transitory and non-selective nature of radicals, with HLF being the exception. Originally, the resolution lay in the serendipitous analysis of a vast multitude of various protecting groups on the nitrogen atom in heptylamine in reaction with ceric ammonium nitrate, which led to some potentially interesting results. Research was performed extensively to reproduce these hits, but it turned out not to be the desirable radical-based δ-functionalized product from proton and carbon NMR. While this project was unsuccessful,

I was able to gain extensive insight into traditional organic synthesis, purification techniques, and characterization of complex molecules.

Around this time, another graduate student, Ethan Wappes, had received exciting results in another project that centered on the cyclization of unbiased amine substrates using much milder conditions to generate a comparable yield to that of the HLF or similar modifications. The basis for this reaction was the creation of iodine *in situ* utilizing sodium iodide and (diacetoxyiodo)benzene (PIDA), which allowed for improved yields because it excludes the harsh halogenating reagents typically used in such oxidations and this expanded the substrate scope to include unbiased substrates that have unactivated C-H bonds.

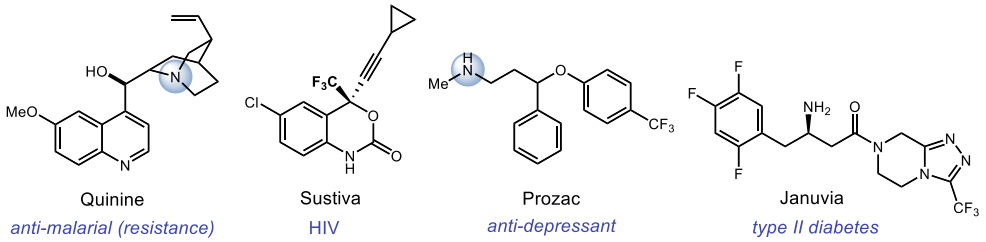
Figure 4. The Direction of the Two Projects



While the lead graduate student focused on the optimization of this method to reproducibly create the best possible yields through numerous screens, I synthesized a number of complex substrates in order to expand the substrate scope to this project. Upon completion, the conditions were relatively optimized and I tested each substrate with the improved conditions, yields were recorded, and characterization via proton NMR, carbon NMR, IR, and high-resolution electrospray ionization (ESI) mass spectrometry was performed to ensure the creation of the ring-closed product.

Upon completion, this method will join the venerable HLF reaction as one of the few synthetic strategies for functionalization at the δ-position in a molecule via C-H activation. This reaction serves as a proof-of-concept that can be applied on a broader spectrum by protecting the amine group of important pharmaceuticals with a protecting group, and then performing the optimized reaction to generate chemically unique derivatives. Thus, the ability to exploit one of the most common bonds in organic chemistry using a single-electron-based mechanism to target the δ-position in a chemio-, regio-, and stereospecific synthetic manner holds great significance in the scientific community, similarly improving the access to chemical diversity in the most accessible classes of molecules in the medicinal and other industrial sectors. For example, it has been illustrated that the bioactivity of medicinal drugs may be enhanced with the incorporation of additional binding motifs.[4] Therefore, in lieu of re-engineering an entire synthetic sequence to obtain analogs of currently approved or under advanced clinical study anti-cancer drug therapies, the expedited method of C-H activation will be applied to study the effects of functionalization at various, selective positions, which may result in increased potency and efficacy. Ultimately, this research demonstrates superb promise because amines are so popular amongst medicinal drugs, having a primary or secondary amine on thirty-seven out of the top fifty pharmaceutical products.[5]

Figure 5. Popular Primary or Secondary Medicinal Candidates



The beneficial development of direct C-H functionalization provides previously inaccessible opportunities for modern synthetic strategies, which can be applied more broadly to

various sectors of society for more expeditious and cost-effective production.[6] For example, the industrial sector may also benefit from the optimization of the anticipated process in numerous applications, such as transitioning the physical state of a chemical into a more transportable state and the synthetic replacement of petrochemical feedstocks by abundant and inexpensive alkanes.[6] The Nagib group is a multifaceted research team composed of three post-doctoral fellows, eight graduate students, and five undergraduate students, dedicating their time to discovering attractive solutions for adaptably selective C-H activation, encompassing radical transition mechanisms. The investigation into this cyclization project has currently submitted a paper for publication. The team on this project has consisted of three members: Ethan Wappes, a second-year graduate student that received his bachelor of science in chemistry from Indiana University; Stacy Fosu, a second-year graduate student that received her Bachelor of Science in chemistry from University of Illinois at Urbana-Champaign and her Master's at the University of Illinois; and myself, Trevor Chopko, who is receiving his Bachelor of Science in biochemistry along with a minor in Russian in December of 2015 from The Ohio State University.

BACKGROUND

Organic molecules typically consist of chains and/or rings of carbon atoms, each covalently bonded to one or more hydrogen atoms and are additionally often garnished with a heteroatom, mostly oxygen, nitrogen, sulfur, phosphorus, or any halogen. Corresponding molecules comprise an expansive array of synthetic molecules, such as petroleum, pharmaceuticals, polymers, and plastics, and biomolecules in living organisms, such as DNA/RNA, carbohydrates, lipids, amino acids, enzymes, coenzymes, and a vast assortment more. Organic synthesis rests in the

transformation of functional groups, typically through the replacement of an atom on the existing substrate, which is entirely dependent upon the duality between thermodynamic and kinetic facets that interplay to generate the most stable configuration of the molecule. In this regard, the carbon-hydrogen bonds are often ignored as a route to the target molecule because of their innately inert nature and high energetic barrier (~100 kcal/mol) that must be overcome in order to introduce a new functional group.[7] Thus, rather indirect multi-step synthetic methods have been developed in order to maintain specific placement of a functional group by targeting carbon-nitrogen, carbon-oxygen, or almost every other carbon bond; whereas direct carbon-hydrogen activation accesses a significantly unexplored synthetic strategy that may unlock the most expeditious synthesis of a desired molecule in a single step.[1,8]

Additionally, generating the ability to selectively target a number of different C-H bonds in a complex substrate allows for undeviating access to a multitude of analogs from that substrate.[7] Traditionally, several multistep approaches in a *de novo* sequence would be developed in order to obtain each derivative. Hence, the capability to harness one of the most common bonds in organic molecules in a rather untapped market holds considerable appeal to the scientific community because of the significant reduction in steps and the ease with which analogous substrates may be acquired. Initial studies looked to nature as means of enlightenment to derive synthetic methods for C-H activation. The compound of enzymes cytochrome P450 is responsible for the metabolism of approximately 75% of known pharmaceuticals through controlled C-H activation.[9-10] These biochemical reactions occur in living organisms with an impeccable level of accuracy in chemio-, regio-, and stereoselectivity and minimal byproducts.[11] Compound I of cytochrome P450 has a thiolate-ligated heme-core that utilizes dioxygen and hydrogen to functionalize biological compounds by hydrolating inactivated C-H bonds.[10] These enzymes serve as a proof-of-concept

that confirms the initial hypothesis and encourages further investigation into this realm through biomimicry.

In the first project focused on δ-functionalization, cerium (IV) ammonium nitrate (abbreviated as CAN) was the first oxidant screened because it is an inorganic molecule that functions as an oxidizing reagent with the potential ability to add a nitrate group to the molecule of interest.[2] Cerium (IV)-based reagents are appealing to chemists because they are mild and far less toxic in comparison with other metal-based reagents and CAN has a relatively high solubility in organic solvents.[2] Additionally, CAN has demonstrated a mild and simple route to C-H activation of hydrocarbons to furnish nitrated products.[2] This reagent is most often used as an oxidant and exploration into its nitrate ester has been limited thus far to only a handful of projects. For example, CAN has demonstrated the ability to selectively perform an oxygenated nitration on the α-carbon of cyclohexene in limited yields, on naphthalene to form 1-nitronapthalene, and on styrene molecules, in addition to a vast multitude of oxidative techniques that displays the versatility of such a powerful, yet seemingly somewhat uncharted reagent.[1,12-13] Generating a direct and efficient manner with which oxygenated nitration can occur in a multifaceted molecule in mild conditions with limited byproducts is restricted and it is believed that an exploration into CAN's capabilities through C-H activation may unlock this goal. This work builds upon prior work accomplished through the radical-mediated Hofmann-Löffler-Freytag reaction, which provided the initiation through which the conception of δ-specific C-H activated oxygenation could be designed.[3] Additionally, the efforts of David Nagib in the development of the first method for the direct C-H trifluoromethylation on aryl and heteroaryl carbons in a single reaction using photoredox catalysts and the work of the Macmillan group on the carbo-oxidation of styrenes using CAN provided a foundation for support.[13-14]

The cyclization project focused its efforts towards improving modifications previously made to the HLF reaction, such as the Suárez Modification or the Muñiz Modification. The original HLF reaction is not ideal because it involves refluxing a halogenated amine substrate in neat strong acid (sulfuric acid), and then quenching with base to generate the pyrrolidine product. Using such a strong acid is incredibly harmful to human health and can also lead to substrate decomposition, but this well-studied reaction and mechanism has allowed for the field of C-H activation to expand exponentially. The Suárez Modification made improvements to the original reaction by replacing the strong acid with iodine gas, PIDA, and a light source. However, iodine is still a harsh oxidant that has the ability to decompose substrates, so this reaction only works on activated C-H bonds. The Muñiz Modification involves utilizing a specialized reagent and a catalytic amount of iodine in the presence of light, but this is still far from useful in most applications because of the necessity to synthesize the specialized reagent and its limitations to only biased substrates. Activated or biased C-H bonds are adjacent to a heteroatom or in the benzylic positions and are therefore electron-deficient or resonance-stabilized, weaker C-H bonds, which allows for easier cleavage due to the reduced activation barrier. Unactivated or unbiased C-H bonds are the typical, normal C-H bonds that are ubiquitous in natural products and pharmaceuticals that require about 100 kcal/mol to cleave. Additionally, the efforts of David Nagib in the development of the first method for the direct C-H trifluoromethylation on aryl and heteroaryl carbons in a single reaction using photoredox catalysts, the work of the Macmillan group on the carbo-oxidation of styrenes using CAN, and the research of Nair and Deepthi in supplying a variety of CAN-based reactions of a multitude of substrates, showcasing the multifaceted elements of CAN, furnished a framework of support.[12-14] The trifluoromethylation of unactivated arenes and heteroarenes by photoredox catalysis displayed the flexibility of direct C-H activation on a diverse range of substrates and

significant insight into strategies based on a radical addition mechanism, analogous to those employed by enzymes. The carbo-oxidation of styrenes explored the sequential C-C bond formation followed by functionalization through the radical intermediate at the newly generated α-position, illustrating the plausibly selective control of CAN. These initial analyses culminated to provide a probable foundation with which the pillars of this project's postulate would presume successful.

The activation of C-H bonds proposes a unique, extraordinary potential for increased synthetic efficiency to complex molecules, which ultimately will lead to a rapid expansion in drug discovery. Current *de novo* synthesis of medicinal molecules is a labor- and resource-intensive task and since there are significant drawbacks to the construction of such complex substrates, the investigation of related chemical analogs is typically excluded.[15] The potency, efficacy, and bioactivity of drug candidates are often increased by targeted functionalization at specific positions, which suggests that chemical-specific functionalization enables desired performance.[4] Presently, a number of synthetic analogs of anti-cancer drug therapies such as taxol, epothilone, and discodermolide are under advanced clinical study.[4] Consequently, an optimized catalytic C-H activation tactic with supreme selectivity would prove beneficial to the medicinal community because numerous chemical analogs could be obtained with increased efficiency. In a single synthetic reaction, proven medicinal molecules can be taken off of the shelves and used as substrate in lieu of re-engineering entire synthetic sequences.[16] Additionally, this strategy could drastically impact the industrial sector of our society by utilizing one of the more abundant and inexpensive chemical groups, saturated hydrocarbons, and turning them into synthetically useful compounds. For example, natural gas is often located in remote locations from where it is mostly consumed, so by converting the hydrocarbon gas, such as methane, into a more transportable liquid, such as

methanol, the transportation costs are drastically reduced and can improve hydrocarbon employment.[16] The development of direct C-H activation has limitless applications in the medicinal, scientific, and industrial sectors of society and offers a rewarding potential for increased effectivity in modern synthetic strategies.

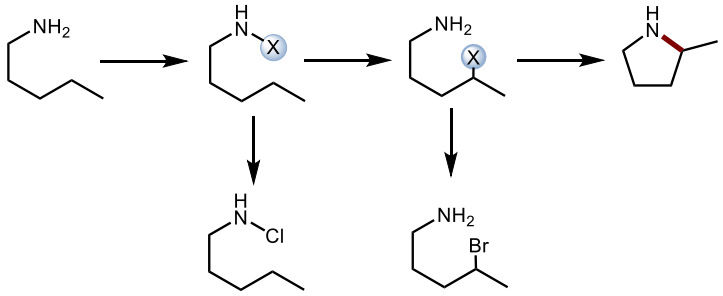
PRELIMINARY STUDIES & RESEARCH METHODOLOGY

The activation of carbon-hydrogen bonds is a popular, but rather uncharted area in modern organic chemistry. Numerous reactions employing this synthetic strategy have been developed; although, a great deal of these reactions often occur in harsh, unfeasible conditions that can only be loosely applicable outside the laboratory. Initially, nature provided the only source of illumination that such inactive bonds could be targeted for direct, selective functionalization through single-electron oxidative mechanisms in Cytochrome P450.[10] Although, enzymes work under physiological conditions in such a way in which they are able to orient themselves upon a molecule to exclude certain factors, such as water or oxidation, from occurring and have the ability to adjust their conformation to ensure that the desired outcome ensues with minimal byproducts.[11] Thus, although this insight provides a greater understanding of C-H activation and serves as a proof-of-concept that the goal is plausible, it is not a feasible solution because of the perpetual limitations within a chemical setting. The hypothesis for this research was derived from the radical-based mechanism of the Hofmann-Löffler-Freytag (HLF) reaction, as depicted in **Figure 3**.[3] This reaction is incredibly unique in that it utilizes radicals as mean of attack, nevertheless targeting the δ-carbon to perform ring closure. The influence of the HLF reaction is evident in this research through the generation of the nitrogen radical, which performs a 1,5-single-electron rearrangement

by abstracting a proton from the δ-carbon through its homolytic cleavage. Although, deviation occurs from the HLF reaction through its interruption, by trapping the intermediary δ-radical on a protected heptylamine derivative with a nitrate provided by cerium (IV) ammonium nitrate, thereby excluding the negative components of harsh halogenation followed by radical initiators in the original reaction. The ability to harness the intermediary radical through the established HLF reaction via interruption in mild conditions would prove valuable by expanding the synthetic toolbox and serving as a template for future reactions with similar mechanisms. However, throughout multiple screenings using a number of substrates, the project proved unsuccessful and it was decided that my efforts were better spent elsewhere.

The cyclization project then focused on utilizing the known mechanism of the HLF to improve its conditions by generating iodine *in situ*. After the initial hit with tosylated heptylamine, the team sought to isolate key intermediates in the reaction.

Figure 6. Isolated Intermediates in the Cyclization Reaction



This ensured that the reaction was creating the nitrogen-centered radical, performing a 1,5-hydrogen-atom abstraction to generate a carbon-centered radical, and then undergoing cyclization. With this background knowledge, the direction of our group was to divvy the project between its members to garner desirable results in the most efficient manner with Ethan Wappes and Stacy Fosu focusing on the optimization of this reaction and I began to prepare a number of subsrates

we knew that we would want to test this method on and expand the substrate scope. After around three months when the reaction was largely optimized and the substrate scope was prepared, we began to test each substrate (following **Figure 7**), purify, and identify whether or not the aliphatic chain closed to form a pyrrolidine ring. If successful, the compounds were characterized via proton NMR, carbon NMR, electrospray ionization high-resolution mass spectrometry, and infrared spectroscopy. A number of additional substrates were tested in order to display the generalization of this procedure to a multitude of potential candidates, such as amino acids, both biased and unbiased C-H bonds, and various protecting groups. This work has led to recent submission for publication, numerous poster presentations, and conference presentations.

ACKNOWLEDGEMENTS

I would like to thank Professor David Nagib for giving me the opportunity and supporting me throughout this research experience. Additionally, I would like to thank Ethan Wappes and Stacy Fosu for working on the cyclization process with me. I would sincerely like to thank Kohki Nakafuku for being my mentor and always assisting me in the research laboratory. Financial support for this research was provided by the Undergraduate Research Office and the Honors and Scholars Department at The Ohio State University.

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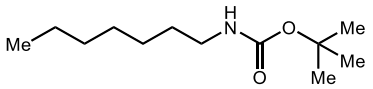
SUPPORTING INFORMATION

General Procedure 1 (GP1): protection of amino acids

Amine (1 eq.) was protected in 50 mL methylene chloride using trimethylamine (1.2 eq.), 4-dimethylaminopyridine (0.1 eq.) and acyl chloride, tosyl chloride, or di-*tert*-butyl dicarbonate (1.5 eq.). It was quenched with dilute hydrochloric acid (1 x 25 mL) and the organic layer washed extracted with methylene chloride (3 x 25 mL). The organic layers were combined, washed with 50 mL of brine, dried over magnesium sulfate, and concentrated in vacuo. It was purified via flash column chromatography using the indicated eluent, yielding specified characteristics.

General Procedure 2 (GP2): tosylation of amino acids

The substrate amino acid (1 eq.) was dissolved in 1.5 M potassium hydroxide. ρ-toluenesulfonyl chloride (1.2 eq.) was dissolved in diethyl ether and this was added to the potassium hydroide solution. This stirred overnight and was quenched with 1 M hydrochloric acid (2 x 30 mL) when the reaction was complete. The aqueous layer was washed with methylene chloride (3 x 25 mL), dried over magnesium sulfate, concentrated in vacuo, and purified via flash column chromatography on silica gel with the indicated eluent. Any changes to this procedure will be specified for each substrate.

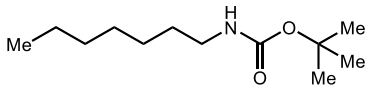


***Tert*-butyl heptylcarbamate:** (Englund EA, Gopi HN, Appella DH. An efficient synthesis of a probe for protein function: 2,3-diaminopropionic acid with orthogonal protecting groups. Org. Lett. 2004. 6(2): 213-215.)

Heptylamine (3.87 mL, 26 mmol) was protected in 50 mL methylene chloride using trimethylamine (5.49 mL, 39 mmol), 4-dimethylaminopyridine (0.150 g, 2.6 mmol) and di-*tert*-butyl dicarbonate (6.81 g, 31 mmol). It was quenched with water (1 x 25 mL) and the organic layer washed extracted with methylene chloride (3 x 25 mL). The organic layers were combined, washed with 50 mL of brine, dried over magnesium sulfate, and concentrated in vacuo. It was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes eluent), yielding a clear oil (4.14 g, 74% yield, R_f = 0.6 in 15% ethyl acetate/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.50 (s, 1H), 3.09 (q, *J* = 6.7 Hz, 2H), 1.43 (s, 12H), 1.33 – 1.21 (m, 9H), 0.87 (t, *J* = 6.9 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.12, 79.10, 40.79, 31.90, 30.22, 29.09, 28.58, 26.90, 22.70, 14.17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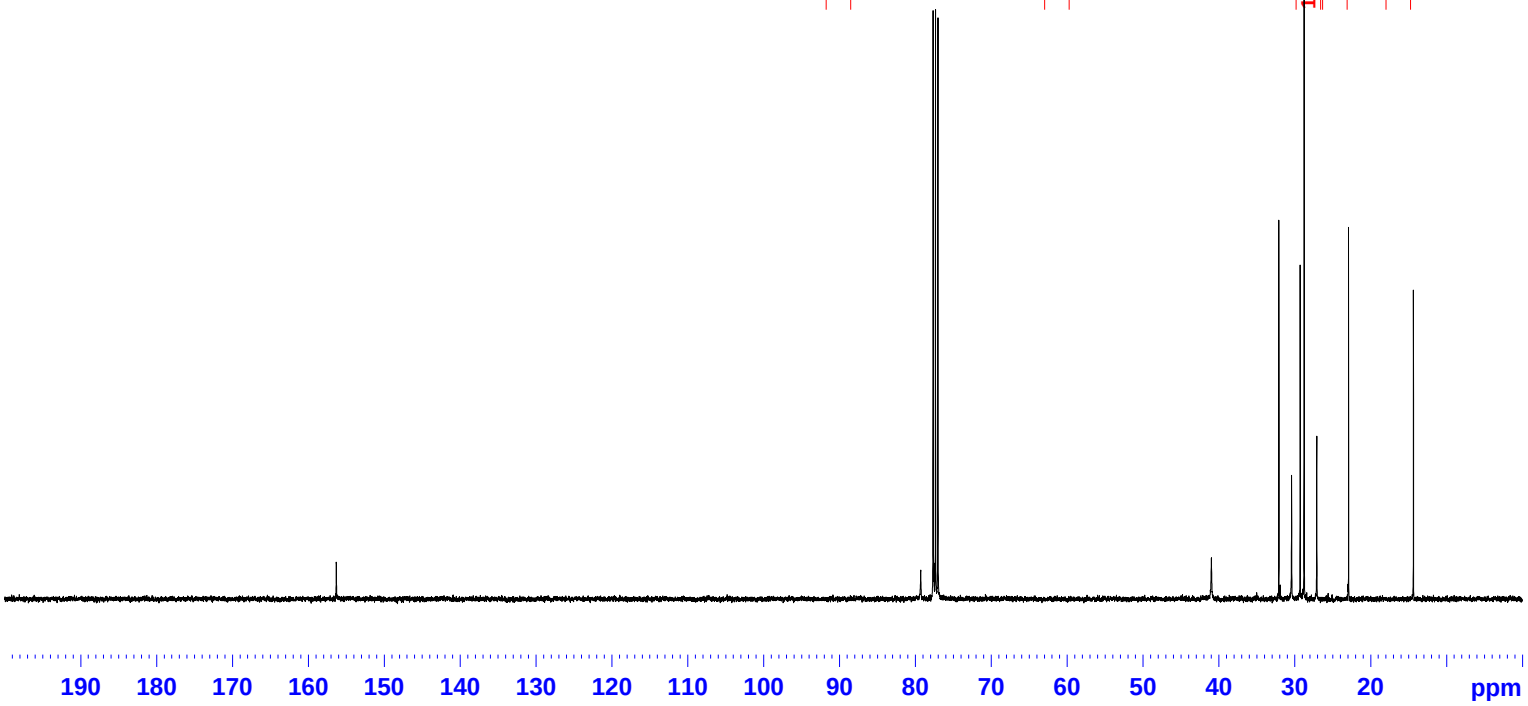
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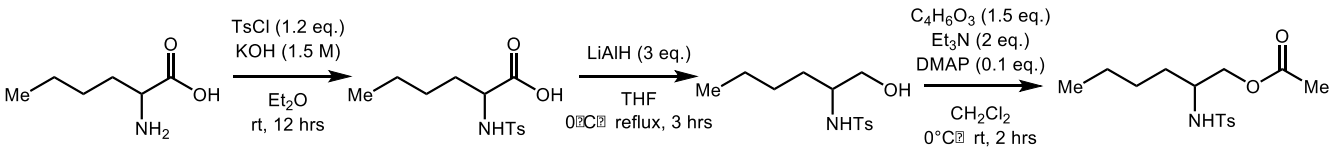
Synthesis of 2-((4-methylphenyl)sulfonamido)hexyl acetate:



Step 1: Tosyl-protection (Li G, Zhao G. 2006. Allylation of aldehydes and imines: promoted by reusable polymer-supported sulfonamide of *N*-glycine. Org. Lett. 8(4). 633.)

Following GP2, the norleucine amino acid (3.0 g, 23 mmol) was protected in 39 mL of 1.5 M potassium hydroxide using ρ-toluenesulfonyl chloride (4.35 g, 27 mmol) that was dissolved in 22.5 mL of diethyl ether to yield the product as a white crystal (3.845 g, 59% yield).

Step 2: Acid reduction (Craig D, Hyland CJT, Ward SE. 2005. Stereoselective γ-lactam synthesis *via* palladium-catalysed intramolecular allylation. Chem. Comm., 27, 3439-3441.)

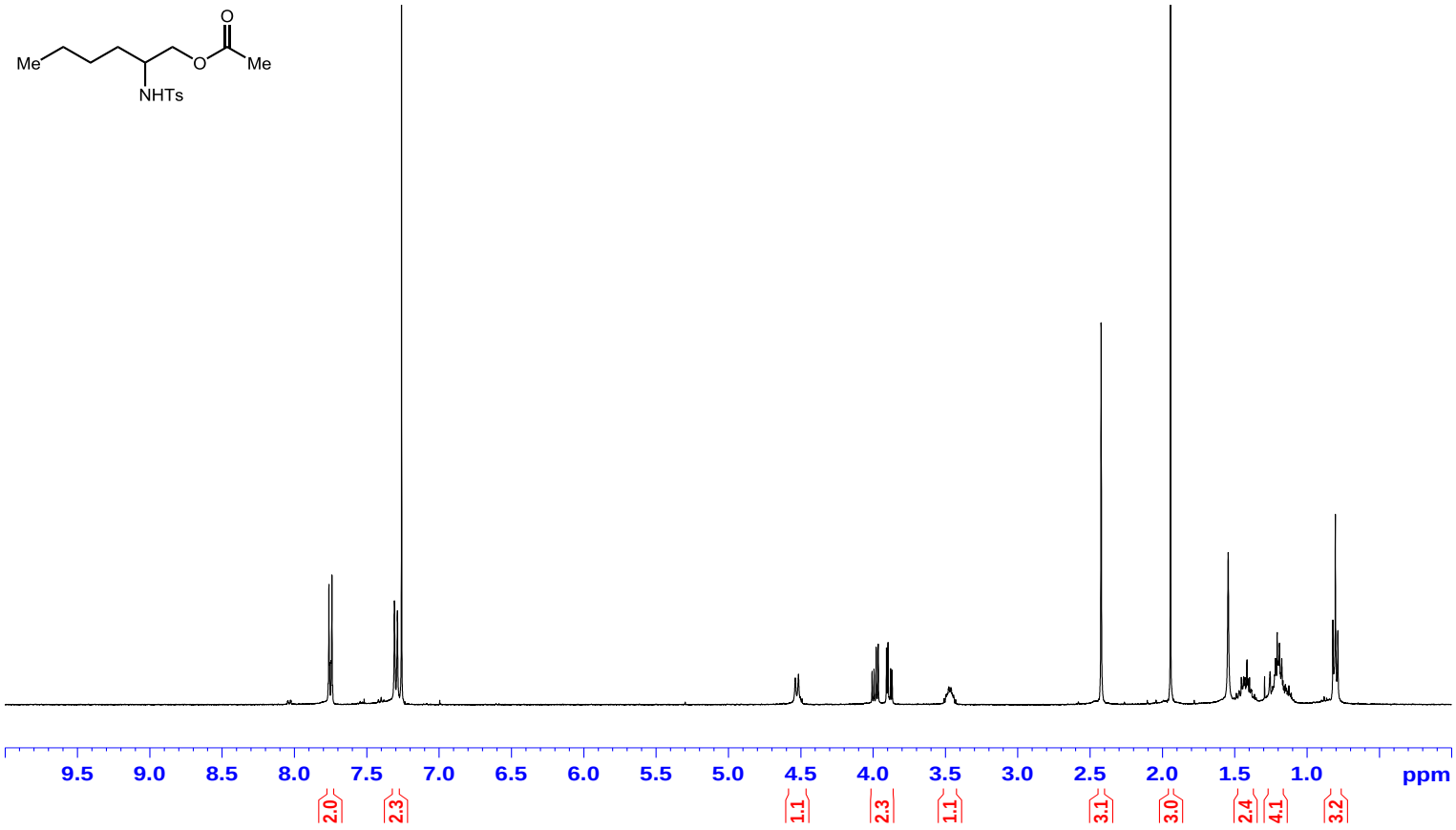
To a solution of the tosylated norleucine (1.0 g, 3.5 mmol) in 16 mL tetrahydrofuran at 0ºC, a solution of 1 M lithium aluminum hydride (0.399 g in 6.4 mL, 11 mmol) was slowly added. The reaction was then brought to room temperature and refluxed for two hours. It was quenched with ethyl acetate, poured into Rochelle's salt (25 mL of a 50% sat. aq. solution), and stirred for one hour. The solution was extracted with ethyl acetate (3 x 25 mL), the combined organic layers were washed with 50 mL of brine, dried with magnesium sulfate, and concentrated in vacuo. Flash column chromatography was performed using a 20% ethyl acetate/hexanes eluent, yielding the product as a clear yellow oil (0.55 g, 55% yield).

Step 3: Acylation (Huber T, Schneider L, Prag, A, Gerhardt S, Einsle O, Muller M. Direct reductive amination of ketones: structure and activity of *S*-selective imine reductases from *Streptomyces*. 2014. Chem. Cat. Chem., 6(8), 2248-2252.)

Following GP1, the tosylated amino-alcohol (0.25 g, 0.92 mmol) was protected in 50 mL methylene chloride using trimethylamine (0.2574 mL, 1.8 mmol), 4-dimethylaminopyridine (0.01126 g, 0.092 mmol), and acetic anhydride (0.1305 mL, 1.4 mmol), which was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes), yielding a clear oil (0.255 g, 88.5% yield, R_f = 0.2 in 20% ethyl acetate/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* =8.1 Hz, 2H), 4.53 (d, *J* = 8.4 Hz, 1H), 4.01 – 3.86 (m, 2H), 3.52 – 3.42 (m, 1H), 2.42 (s, 3H), 1.94 (s, 3H), 1.49 – 1.35 (m, 2H), 1.30 – 1.08 (m, 4H), 0.80 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.60, 143.22, 137.93, 129.46, 126.83, 65.60, 52.68, 31.96, 27.29, 22.08, 21.29, 20.43, 13.58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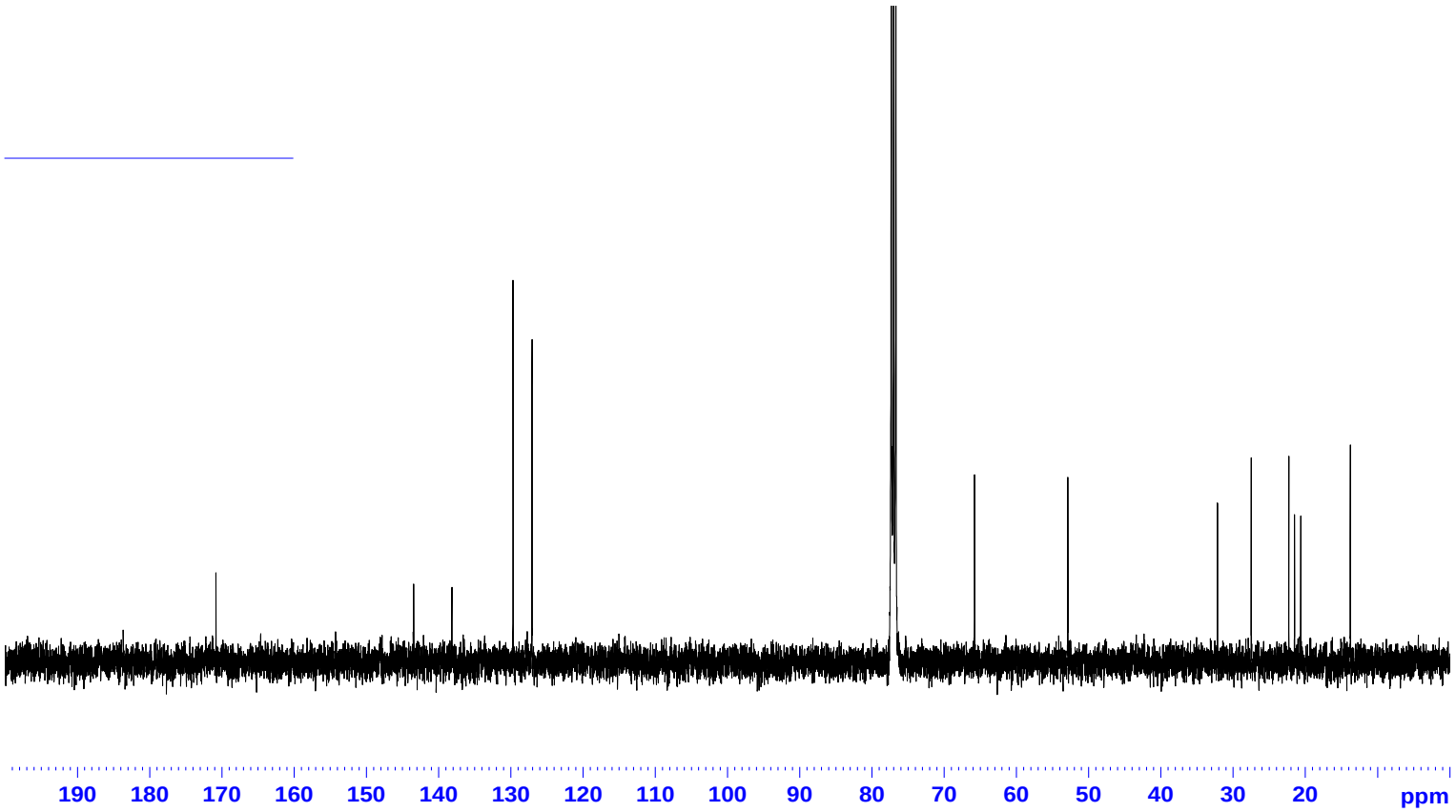
4.1
3.2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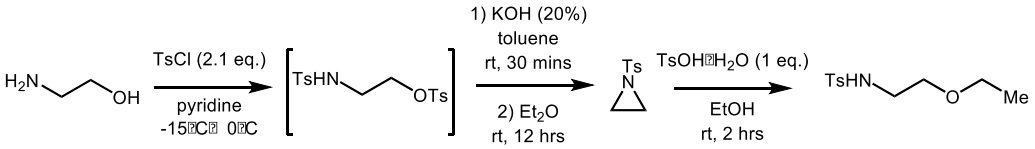
ppm

Synthesis of N-(2-ethoxyethyl)-4-methylbenzenesulfonamide:



Step 1: Aziridine creation (Fleming A. 2005. Novel chemistry of tetrahydropyridines [dissertation]. University of London.)

To a solution of ρ-toluenesulfonyl chloride (16.58 g, 87 mmol) in pyridine (10 mL) at -15ºC, ethanolamine (2.5 mL, 41 mmol) was added dropwise and stirred for two hours at -15ºC. The reaction was then brought to 0ºC and stirred at this temperature for four hours. The reaction was then transferred to the freezer and left overnight. A mixture of ice-water was added and the residue was filtered off. The remaining solid was dissolved in 100 mL of chloroform, washed with water (3 x 70 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was recrystallized from chloroform.

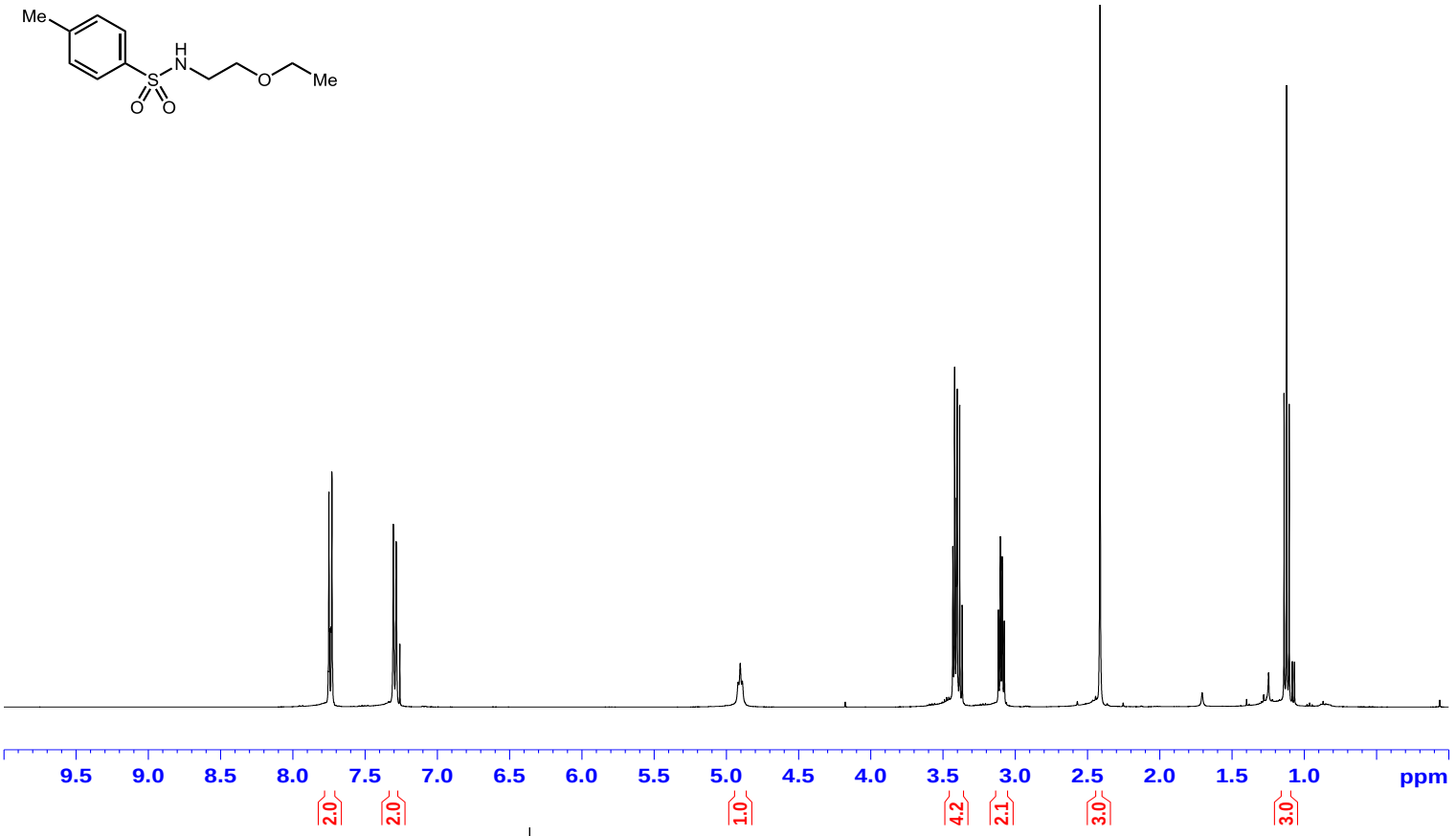
The bis(toluene-4-sulfonyl) aminoethanol was dissolved in 32 mL of toluene at room temperature and a solution of KOH (20% in water, 7 mL, 205 mmol) was added. The biphasic mixture was rapidly stirred for thirty minutes. The organic layer was extracted with methylene chloride (2 x 15 mL), washed with water (15 mL), dried with magnesium sulfate, and concentrated in vacuo. The brown remaining solid was stirred in 25 mL of diethyl ether overnight and then removed under reduced pressure to yield yellow crystals (6.7 g, 82% yield).

Step 2: Aziridine opening

The tosyl-protected aziridine (0.050 g, 0.25 mmol) was dissolved in 4 mL ethanol at room temperature and ρ-toluenesulfonic acid monohydrate (0.0437 g, 0.25 mmol) was added. The reaction stirred for two hours, was washed with water (1x 50), and concentrated in vacuo. It was purified via flash column chromatography (silica gel, 30% ethyl acetate/hexanes eluent), yielding a whitish yellow oil (0.0387 g, 63% yield, R_f = 0.2 in 15% ethyl acetate/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.78 (d, *J* = 6.0 Hz, 1H), 3.45 – 3.38 (m, 4H), 3.11 (q, *J* = 5.2 Hz, 2H), 2.43 (s, 3H), 1.14 (t, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.19, 136.79, 129.49, 126.90, 68.18, 66.30, 42.94, 21.29, 14.78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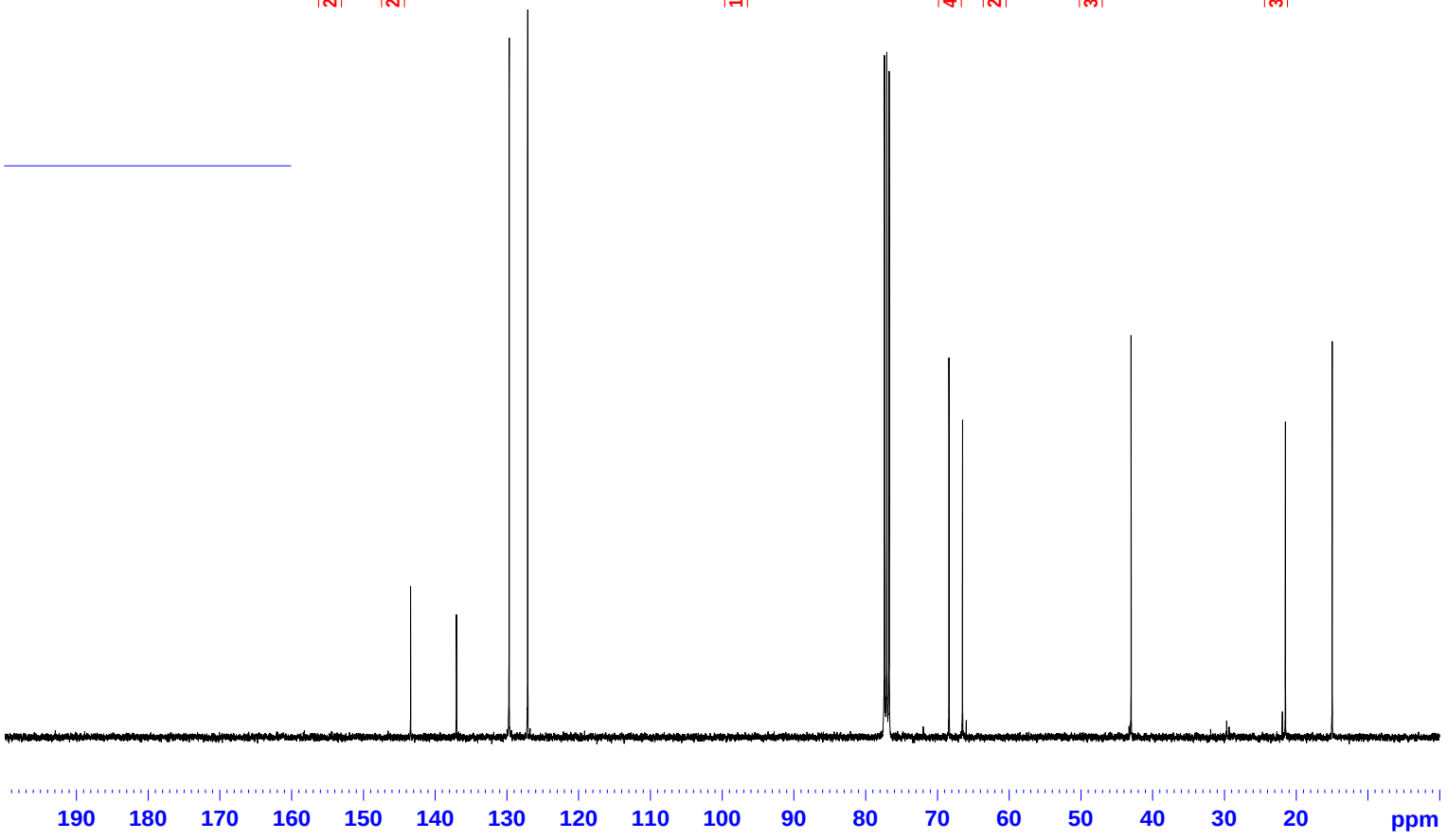
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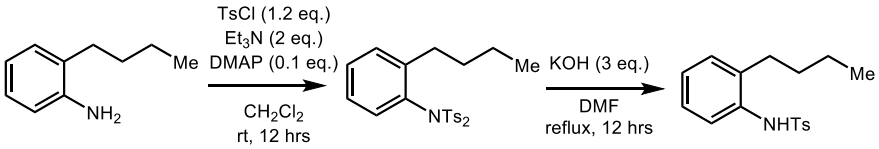
Synthesis of N-(2-butylphenyl)-4-methylbenzenesulfonamide:



Step 1: Bis-tosylation

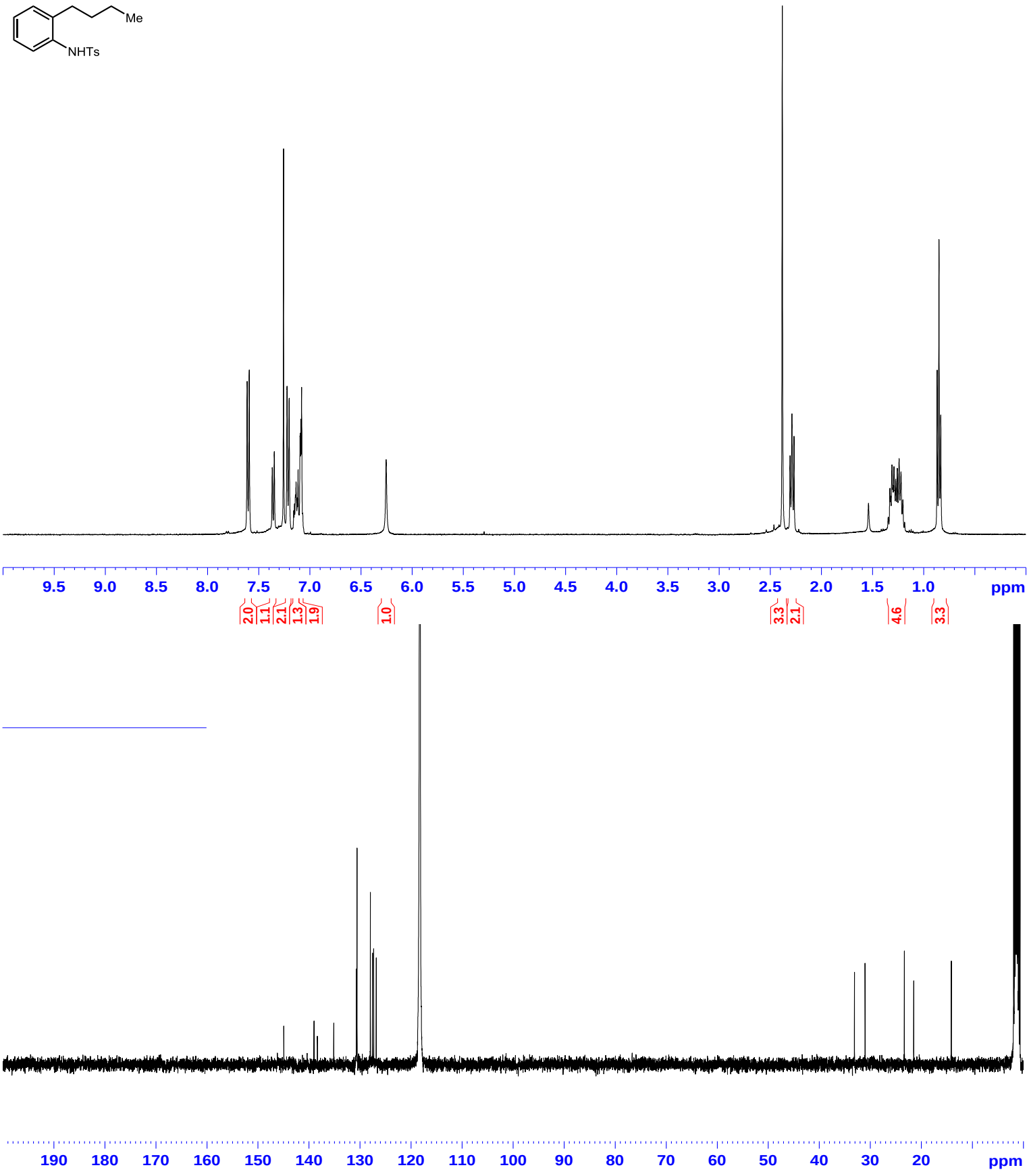
Following GP1, 2-butylaniline (1.05 mL, 6.7 mmol) was protected in 25 mL methylene chloride using trimethylamine (1.87 mL, 13 mmol), 4-dimethylaminopyridine (0.082 g, 0.67 mmol), and ρ-toluenesulfonyl chloride (1.533 g, 8 mmol) to yield brown oil (2.786 g, 91%). The material was carried forth without further purification.

Step 2: Single deprotection

To a solution of the N-(2-butylphenyl)-4-methyl-N-tosylbenzenesulfonamide (1.00 g, 2.2 mmol) in 45 mL dimethylformamide at room temperature, potassium hydroxide (0.3682 g, 6.6 mmol) was added. The solution was refluxed for overnight. The reaction was allowed to cool, 50 mL of water was added, and stirred for thirty minutes. The organic layer was extracted with methylene chloride (3 x 50 mL), washed with brine (1 x 100 mL), dried with magnesium sulfate, and concentrated in vacuo. It was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes eluent), yielding a white crystal (0.625 g, 95% yield, R_f = 0.4 in 15% ethyl acetate/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.17 – 7.06 (m, 3H), 6.25 (s, 1H), 2.38 (s, 3H), 2.29 (t, *J* = 7.3 Hz, 2H), 1.36 – 1.18 (m, 4H), 0.85 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.85, 129.73, 127.33, 127.00, 126.29, 124.34, 32.16, 30.65, 22.66, 21.66, 13.97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2.0 1.1 2.1 1.3 1.9 1.0 3.3 2.1 4.6 3.3
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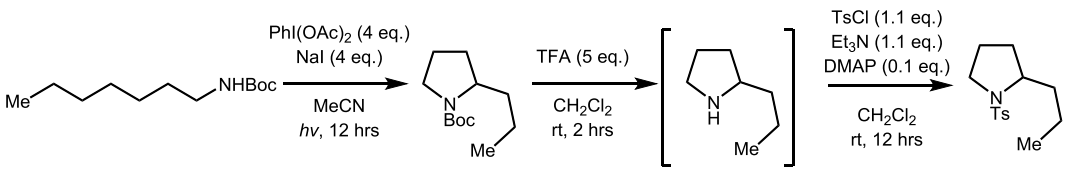
***Tert*-butyl 2-propylpyrrolidine-1-carboxylate to 2-propyl-1-tosylpyrrolidine:**



Step 1: Pyrrolidine formation

Tert-butyl heptylcarbamate was subjected to the general reaction conditions with the exception that the reaction ran for twelve hours. The solution was worked up according to the general procedure and the crude mixture was carried through to the next step.

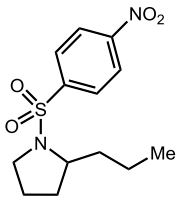
Step 2: Boc deprotection

To the crude mixture, 1 mL of methylene chloride and 1 mL of trifluoroacetic acid was added and the solution was stirred for two hours until complete. The crude mixture was carried through to the next step.

Step 3: Tosylation

Following GP1, the deprotected propyl pyrrolidine in methylene chloride and trifluoroacetic acid was protected using trimethylamine (1.87 mL, 0.26 mmol), 4-dimethylaminopyridine (0.003 g, 0.022 mmol.), and ρ-toluenesulfonyl chloride (0.462 g, 0.22 mmol), which was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes eluent), yielding a clear oil (1.01 g, 20%).

The ^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$), and HRMS (ESI) *m/z* match that of the tosyl-protected heptylamine ring-closure.



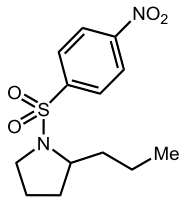
1-((4-nitrophenyl)sulfonyl)-2-propylpyrrolidine:

Nosyl-protected heptyl was subjected to the general reaction conditions with the exception that the reaction ran for five hours. It was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes eluent), yielding a clear oil (0.255 g, 51%, R_f = 0.4 in 15% ethyl acetate/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.9 Hz, 2H), 8.02 (d, *J* = 8.9 Hz, 2H), 3.70 – 3.62 (m, 1H), 3.47 – 3.39 (m, 1H), 3.26 – 3.17 (m, 1H), 1.90 – 1.76 (m, 2H), 1.66 – 1.59 (m, 2H), 1.59 – 1.40 (m, 2H), 1.39 – 1.27 (m, 2H), 1.33 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.14, 144.30, 128.65, 124.41, 61.02, 49.02, 38.51, 30.83, 24.29, 19.46

HRMS (ESI) *m/z*: calculated for 321.0886 (with the addition of one sodium ion is 321.0885 so there is a 3.114×10^{-7}% error)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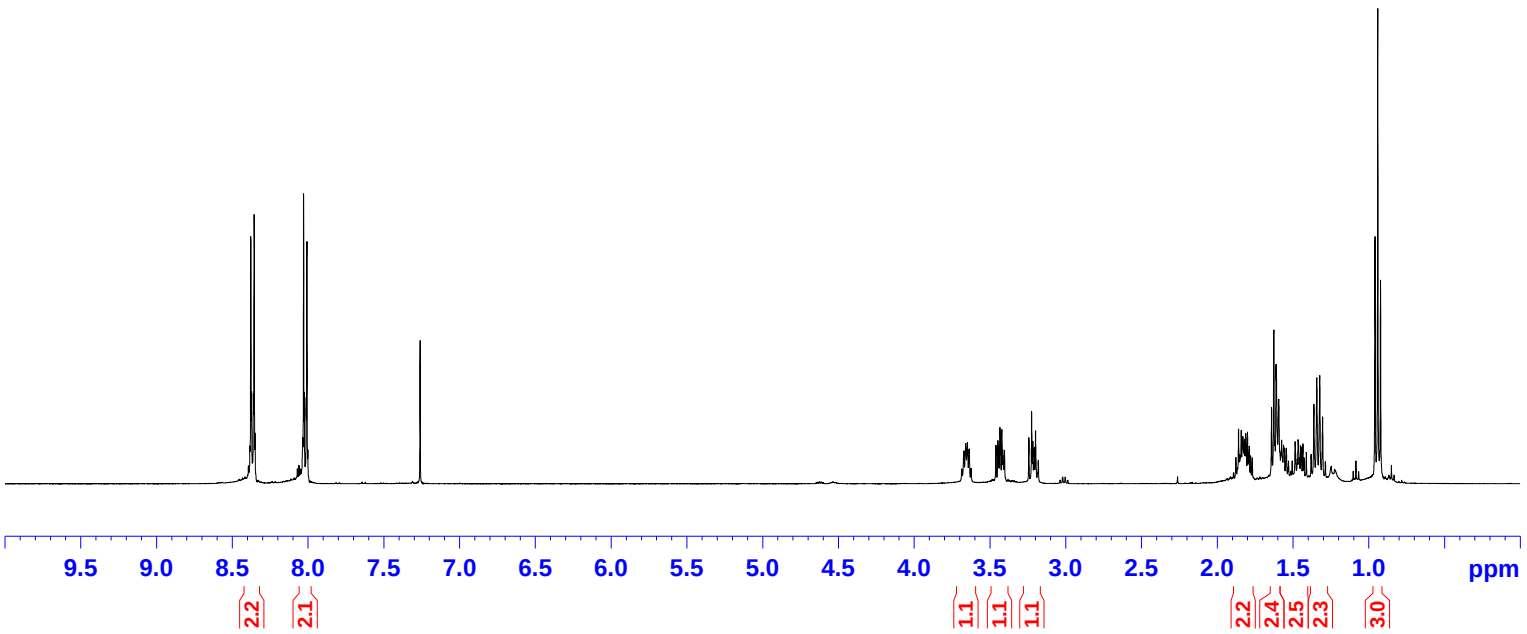
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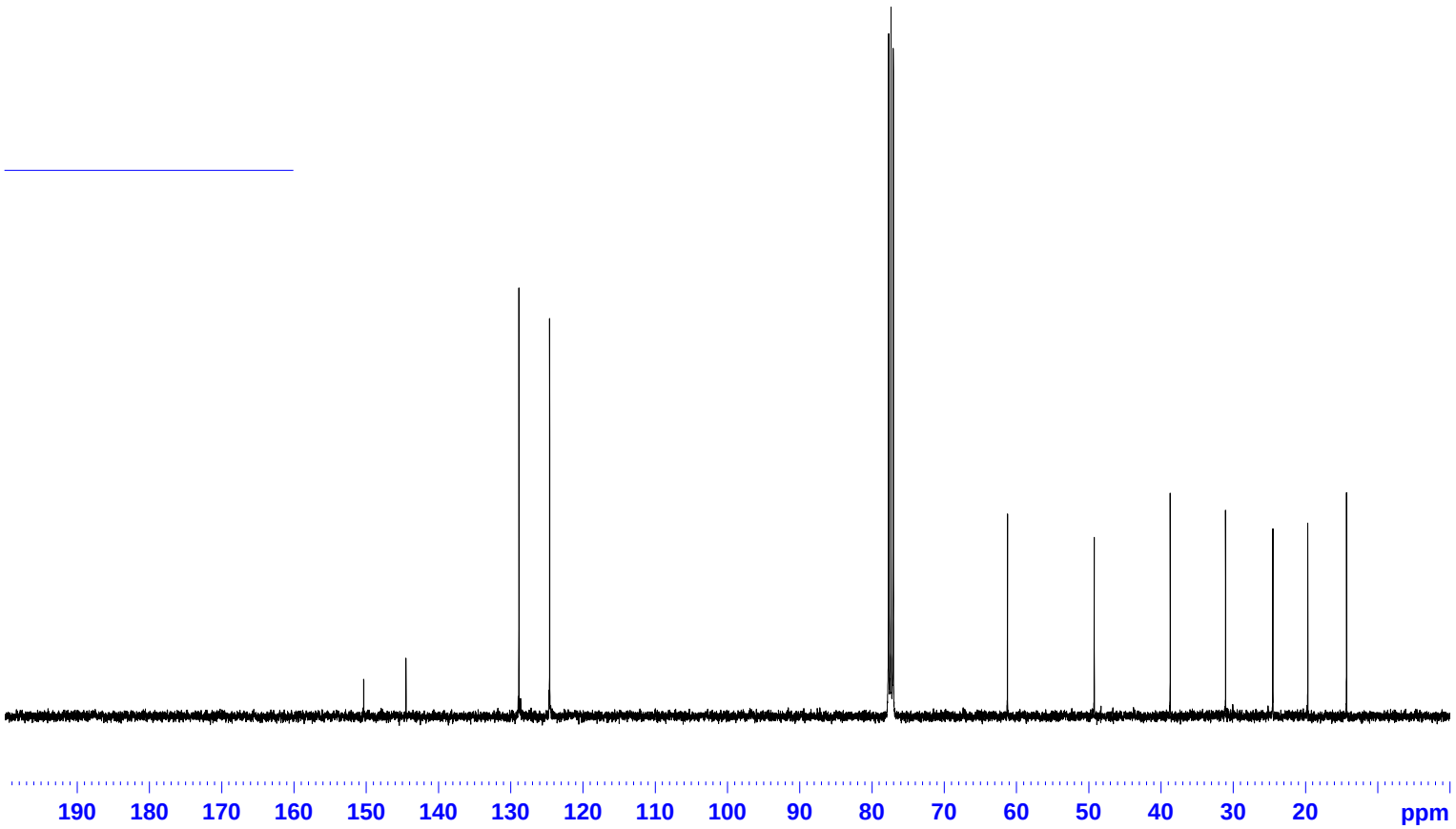
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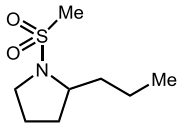


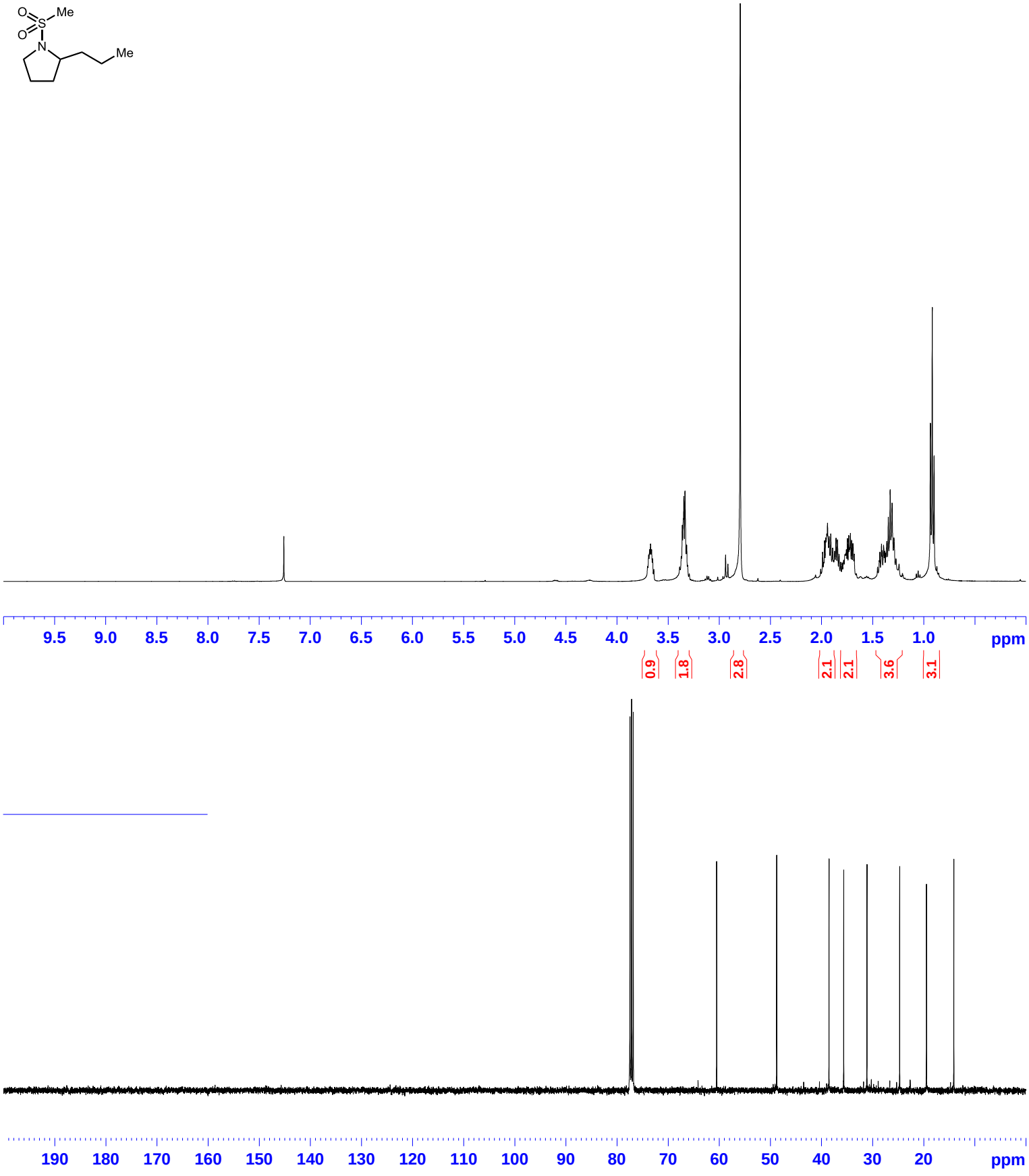
1-(methylsulfonyl)-2-propylpyrrolidine:

Mesyl-protected heptyl was subjected to the general reaction conditions with the exception that the reaction ran for four hours. It was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes eluent), yielding a clear oil (0.0233 g, 46%, R_f = 0.3 in 15% ethyl acetate/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.72 – 3.63 (m, 1H), 3.41 – 3.28 (m, 2H), 2.79 (s, 3H), 2.02 – 1.89 (m, 2H), 1.81 – 1.66 (m, 2H), 1.47 – 1.21 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.30, 48.56, 38.33, 35.45, 30.90, 24.50, 19.25, 13.90

HRMS (ESI) *m/z*: calculated for 192.1070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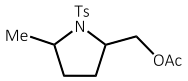
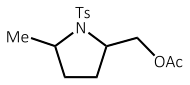


(5-methyl-1-tosylpyrrolidin-2-yl)methyl acetate:

The acylated norleucine derivative was subjected to the general reaction conditions with the exception that the reaction ran for five hours. It was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes eluent), yielding a whitish crystal (0.0166 g, 37%, R_f = 0.3 in 15% ethyl acetate/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 4.22 – 4.10 (m, 2H), 3.92 – 3.85 (m, 1H), 3.67 (q, *J* = 6.4 Hz, 1H), 2.43 (s, 3H), 1.72 – 1.63 (m, 2H), 1.56 – 1.46 (m, 2H), 1.34 (d, *J* = 6.1 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.85, 143.60, 134.93, 129.80, 127.69, 66.63, 59.55, 57.79, 32.30, 27.37, 23.07, 21.62, 21.00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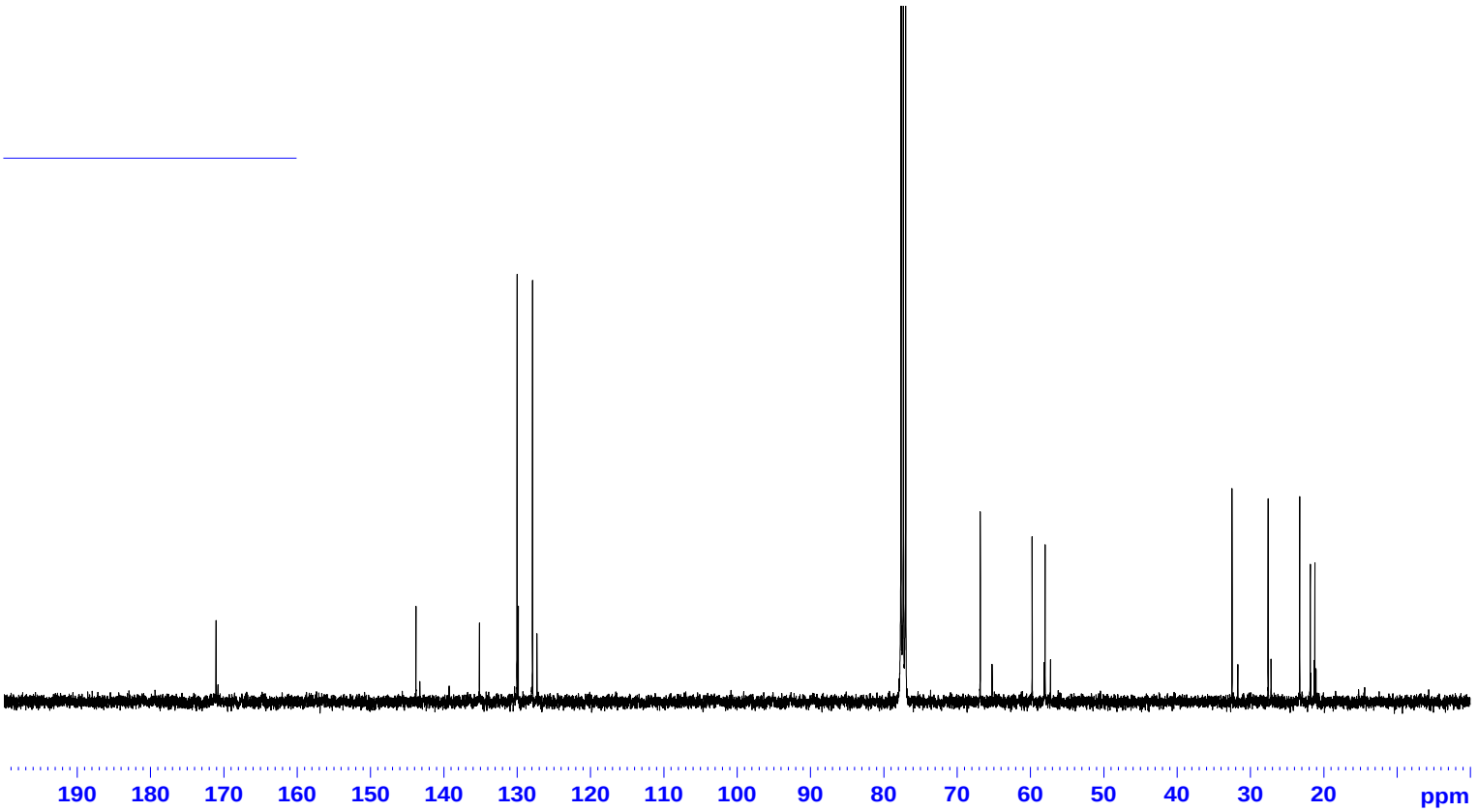
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